

ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #635

1. Title:

Multiple Metabolic Syndrome and Carotid IMT

2. Writing Group:

(lead) Golden, Coresh, Folsom, Sharrett, Szklo, Brancati

3. Timeline:

Can begin immediately since analysis is limited to baseline data.

4. Rationale:

Although CVD risk factor clustering had been observed for many years, it wasn't until 1988 that several of these factors were formally grouped together under the rubric of "Syndrome X" by Reaven. Since 1998, various authors have also hypothesized a syndrome of clustered CVD risk factors, sometimes called "Insulin Resistance Syndrome" or the "Multiple Metabolic Syndrome" (MMS). For example, a previous study in ARIC has demonstrated clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension, which was independently associated with fasting insulin, waist-hip ratio, and BMI (Schmidt, 1996). Most definitions of MMS include hyperinsulinemia, hypertension, hypertriglyceridemia, decreased HDL, and obesity (Godsland, 1995; Opara, 1997; Haffner, 1997; Ruderman, 1998; Meigs, 1997), but the various definitions do differ in number and type of component abnormalities.

MMS has recently attracted a good deal of research attention insofar as it may represent a pathophysiologic "common soil" for both type 2 diabetes and atherosclerotic CVD. A vast literature relates individual components of MMS to CVD risk. In addition, a few investigators have studied the cross-sectional relationship of insulin resistance (measured using clamp techniques) with carotid IMT (Laakso, 1991; Howard, 1996). However, most previous studies of MMS per se have been confined to cross-sectional studies of risk factor clustering without reference to atherosclerotic end-points.

Thus, the importance of MMS per se for CVD risk is uncertain. Moreover, there is currently no empirical basis for comparing various definitions of MMS in terms of CVD risk. If the risk of atherosclerosis in MMS is no greater than the risk predicted by the sum (or product) of its individual components, then the need for further investigation / definition of this entity is reduced--rather one should simply focus on the individual components. If, instead, MMS is associated with an excess risk of atherosclerosis beyond what would be predicted by its individual components, this would support the notion of MMS as a distinct pathophysiologic entity, worth of additional research, and perhaps clinical attention as a marker of especially high risk.

5. Main Hypothesis:

At baseline, "MMS" will be independently associated with carotid IMT after simultaneous adjustment for its individual components.

At least 3 definitions will be used:

(a) Reaven's definition: hyperinsulinemia, hyperglycemia, hypertension, hypertriglyceridemia, low HDL

(b) Meigs' definition (central metabolic syndrome): hyperinsulinemia, hypertriglyceridemia, low HDL, central obesity

(c) Consensus definition: hyperinsulinemia, hypertension, hypertriglyceridemia, low HDL, central obesity

6. Design:

Cross-sectional analysis of baseline metabolic characteristics and carotid artery intimal media thickness in non-diabetic individuals

7. Data:

Baseline fasting insulin levels, fasting glucose, blood pressure, triglycerides, HDL, waist-hip ratio, BMI, glucose tolerance status, age, gender, race, medical history, medications, smoking status, coronary heart disease status; carotid artery intimal media thickness

Tentative Cut-offs for Components:

Hypertension SBP>140 mmHg
DBP>90 mmHg
Or on medication for hypertension

Low HDL <35 mg/dL in men
<45 mg/dL in women

Elevated TG >200 mg/dL

Obesity BMI>27.3 kg/m² in women
BMI>27.8 kg/m² in men

Elevated Insulin >140 pmol/L (fasting)

Hyperglycemia 110-125 mg/dL (ADA "impaired fasting glucose")

8. Analysis:

Multiple linear regression, with carotid IMT as the dependent variable; MMS as the independent variable; and dichotomized BMI, BP, HDL, TG, glucose, and fasting insulin as the covariates (as well as age, sex, race, center, etc.). Parallel regressions will be run for different definitions of MMS. Regardless of MMS definition, however, the same set of covariates will be used. If power allows, we will also do analyses stratified by race, in light of work from the IRAS study suggesting differences in the relationship of insulin resistance to IMT in blacks vs whites.